The Radioactive Drug Research Committee (RDRC): A 2005 Update

Society of Nuclear Medicine
Toronto, Canada
June 19 - 22, 2004

O H Suleiman, R Fejka, M Walsh
Center for Drug Evaluation and Research
Office of New Drugs

FDA Public Meeting "Radioactive Drugs for Certain Research Uses"
(November 16, 2004)

1. Pharmacological Dose Limits
2. Radiation Dose Limits
3. Pediatric Research Subjects
4. Quality and Purity of Radiopharmaceuticals
5. RDRC Membership & Administrative Issues

For transcripts and meeting presentations go to: WWW.FDA.GOV, and search on "RDRC November 16"

Human Research with an Investigational New Drug application (IND) versus RDRC

RDRC research is:

- Basic science for advancing knowledge, such as biodistribution of radioactive drug (including kinetics, distribution, localization, physiology, or biochemistry).

- Not intended…
  - for immediate therapeutic or diagnostic benefit or
  - to determine the safety or effectiveness of a drug in humans (requires an IND)

RDRC Radiation Dose Limits

Why do we need to revisit radiation dose limits?

- Based on 1975 occupational dose limits
- Evolving Metrics
- New radiation risk concepts - E
- New scientific data
- New pediatric human research regulations

E, effective dose

RDRC Radiation Dose Limits*

Organ or System	Single Dose	Annual and Total Dose
Whole body	0.03 Sv (3 Rem)	0.05 Sv (5Rem)
Active blood-forming organs	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Lens of the eye	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Gonads	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Other organs	0.05 Sv (5 Rem)	0.15 Sv (15 Rem)

For research subjects under 18 years of age at his last birthday, the radiation dose does not exceed 10 percent of adult dose.

Radiation doses from x-ray procedures that are part of the research study shall also be included.

*21 CFR 361.1 (b) (3)

Rationale for adopting Occupational Dose Limits

- "An informed potential research subject is able to make a decision…and assume a risk in the same sense as does a radiation worker."

- "…that the radiation dose, even though it is within the limit, should be the smallest amount needed to carry out the study"* (ALARA – as low as reasonable achievable)

*Federal Register 31298 Volume 40 Number 144 (July 25, 1975)

Evolving Metrics

1975 RDRC Dose limits- rem
1977 ICRP* promulgates effective dose equivalent, H.
1980's rad to Gray; rem to Sievert; mCi to MBq.
1991 NRC** adopts H for radiation dose
1991 ICRP replaces H with effective dose, E.
1993 NCRP*** adopts E.
2004 ICRP proposes modification of E.

*International Commission on Radiological Protection
**Nuclear Regulatory Commission
*** National Council on Radiation Protection and Measurements

Effective dose (E): A homogenized single metric of radiation risk

Risk based metric, relating partial body irradiations (individual organ or tissue, limited x-ray field) to uniform whole body irradiation.

The effective dose (E) is the sum of the weighted equivalent doses in all the tissues and organs of the body.

$$E = \sum_T W_T H_T$$

W_T is the weighting factor for tissue T, and
H_T is the individual tissue or organ dose for tissue T

***International Commission on Radiological Protection ICRP Report 60, (1991)**

Effective Dose (E)

Tissue Weighting Factors (w_t)

Organ (Tissue)	ICRP 26 1977	ICRP 60 1991	ICRP-DRAFT 2004
Gonads	0.25	0.20	0.05
Breast	0.15	0.05	0.12
Red BM, lung	0.12	0.12	0.12
Thyroid	0.03	0.05	0.05
Bone surfaces	0.03	0.01	0.01
Colon, stomach	NC	0.12	0.12
Bladder, liver, esophagus	NC	0.05	0.05
Skin	NC	0.01	0.01
Salivary glands, brain	NC	NC	0.01
Remainder	0.30	0.05	0.10

Adult Effective dose (E)

Radiation Source	Effective Dose (E)	Equivalent to # of chest x-rays	Equivalent time	Lifetime* Cancer Mortality Risk
		Background		
U.S. - 1 year	3 mSv	150	1 year	$1.5\ 10^{-4}$
		Medical		
Chest x-ray	0.02 mSv	1	2.4 days	$1.0\ 10^{-6}$
Upper GI fl	3 mSv	150	1 year	$1.5\ 10^{-4}$
CT- abdomen	10 mSv	500	3.3 years	$5.0\ 10^{-4}$
Tc-99m-lung perf	1 mSv	50	4 months	$5.0\ 10^{-5}$
Tc-99m-bone	4 mSv	200	1.3 years	$2.0\ 10^{-4}$
PET–FDG	10 mSv	500	3.3 years	$5.0\ 10^{-4}$
		Regulatory Limits		
Individual Gen pop	1 mSv	50	4 months	$5.0\ 10^{-5}$
Worker	50 mSv	2500	16.7 years	$2.5\ 10^{-3}$
Emergency Worker	500 mSv	25,000	167 years	$2.5\ 10^{-2}$
		RDRC Limits		
Whole body	50 mSv	2500	16.7 years	$2.5\ 10^{-3}$
RBM** (50 x .12) =	6 mSv	300	2.0 years	$3.0\ 10^{-4}$

*ICRP risk coefficients

**RBM = Red Bone marrow; $(H_{RBM} \times w_t) = E$

We asked…

- Are current dose limits for adults still appropriate for research conducted under 361.1 ?
- If not, what dose limits are appropriate?
- Should there be different dose limits for different adult age groups?

Pediatric Effective Dose (E)

Radiation Source	Effective Dose (E)	Equivalent to # of chest x-rays	Equivalent time	Lifetime* cancer Mortality Risk
		Background		
U.S. - 1 year	3 mSv	150	1 year	$1.5\ 10^{-4}$
		Medical		
Chest X-ray -child	0.02 mSv	1	2.4 days	$1.0\ 10^{-6}$
PET FDG adult**	8 mSv	400	2.67 years	$4.0\ 10^{-4}$
PET 10year old**	6.4 mSv	320	2.13 years	$3.2\ 10^{-4}$
PET 5 year old**	5.6 mSv	280	1.87 years	$2.8\ 10^{-4}$
		Regulatory Limits		
Individual Gen pop	1 mSv	50	4 months	$5.0\ 10^{-5}$
		Pediatric RDRC Limits		
Whole body	5 mSv	250	1.67 years	$2.5\ 10^{-4}$
RBM*** (5 x .12) =	0.6 mSv	30	2.4 months	$3.0\ 10^{-5}$

*ICRP risk coefficients

**Stabin MG, Gelfand MJ. Q J Nuclear Med 1998:42:93-112.

***RBM = Red Bone marrow; $(H_{RBM} \times w_t) = E$

Pediatric ethics and risks

- **Pediatric Ethics* – 21 CFR Part 50 Protection of Human Subjects**
  Subpart D Additional Safeguards for Children in Clinical Investigations

- **Higher risk for children**
  "…, a new finding is that relative risks decline with increasing attained age, as well as being highest for those exposed as children as noted previously."**

- **Noncancer risk**
  "The evidence for radiation effects on noncancer mortality remains strong, with risks elevated by about 14% per sievert during the last 30 years of follow-up. Statistically significant increases are seen for heart disease, digestive diseases, and respiratory diseases."**

- **Work in progress**
  "People exposed prior to age 20 comprise the largest portion (41%) of the cohort and most of these are still alive.."; "Because our risk models suggest that excess rates (particularly for cancer) are highest for those exposed as children, we anticipate that 60 to 70% of the radiation-associated deaths in the LSS cohort have yet to occur."**

***66 FR 20598, April 24, 2001.**

**Preston et al. Studies of Mortality of Atomic Bomb Survivors Report 13: Solid Cancer and Noncancer Mortaltiy: 1950-1997. Radiation Research 160, 381-407 (2003)

We asked…

- Does 361.1 provide adequate safeguards for pediatric subjects? If yes…
- Do current radiation dose limits for pediatric subjects pose a significant risk?
- If not, what dose limits would be appropriate to ensure no significant risk?
- Should there be different dose limits for different pediatric age groups?

What's else has been happening?

- RDRC Web site - go to FDA.GOV, search on "RDRC web site"
- New Forms 2914 and 2915
- Pending Draft Guidance
- Consider New/Changes Regulations for 21 CFR 361.1
- SNM Sessions – 2004, 2005
- DIA Sessions – 2005

New Initiatives

- FDA's Critical Path Initiative to develop new drugs, inherently dependent on imaging.
- Microdosing – "Human Phase 0" trials – similar to RDRC research but may require an IND.
- Exploratory IND – Recently issued draft guidance (FR 19764 April 14, 2005) for comment (deadline of mid July, 2005). Allows screening of candidate drugs using microdose quantities with limited preclinical studies.

In closing

- Work in progress – go to FDA.GOV, search on keywords
- **Public comment periods still open for RDRC (July 11,2005) and Exploratory IND (July 13, 2005).**
- **FDA Session: Monday 8:00 – 9:30 AM (Room 714 A/B)**

The Future
FDA Campus @ White Oak, Silver Spring, Maryland

Most frequently reported radionuclides

In 2003, 84 FDA approved RDRC's conducted 284 studies with 2797 human subjects

Imaging nuclides		Non-imaging nuclides
Positron (77.1%)	Gamma (4.5%)	Beta (18.4%)
C-11 (36.6%)	Tc-99m (2.5%)	H-3 (12.4%)
F-18 (19.0%)	I-123 (1.3%)	C-14 (4.0%)
O-15 (17.5%)		Fe-59 (0.7%)
N-13 (2.6%)		Ca-45 (0.3%)
Cu-60 (0.7%)	I-131 (0.3%)	Fe-55 (0.3%)
F-17 (0.5%)	Xe-133 (0.3%)	I-125 (0.3%)
Tc-94m (0.2%)	In-111 (0.2%)	Ca-47 (0.2%)
"Gold" < 1.0 %	"White > 1.0 %	Zn-65 (0.2%)

Over 120 different compounds were labeled

Three ways to study radioactive drugs in human subjects:

- 21 CFR 312 Investigational New Drug Application (IND)
- 21 CFR 312.2 Exempt from IND requirements
- 21 CFR 361 Prescription Drugs For Human Use Generally Recognized as Safe and Effective and not Misbranded: Drugs Used in Research
  - 361.1 Radioactive drugs for certain research uses

RDRC Radiation Experience*

- Organ doses are the limiting constraint, not whole body limits.
- Reports suggest general compliance with radiation dose limits.

*** Review of RDRC Annual reports**